

## **Stem cell factor and granulocyte colony-stimulating factor promote neuronal network remodeling and function through VEGF-mediated angiogenesis in a mouse model of CADASIL**

Suning Ping, Xuecheng Qiu, Michele Kyle, Karen Hughes, John Longo, Li-Ru Zhao  
Department of Neurosurgery, SUNY Upstate Medical University, Syracuse, New York, USA

Cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL), a NOTCH3 gene mutation-induced cerebral small vascular disease, is characterized by progressive degeneration of vascular smooth muscle cells (VSMCs) in cerebral small arteries, leading to ischemic stroke and vascular dementia. There is currently no treatment that can slow the progression of CADASIL. We have recently demonstrated the efficacy of combined two hematopoietic growth factors, stem cell factor and granulocyte colony-stimulating factor (SCF+G-CSF) in improving cognitive function and increasing cerebrovascular density (angiogenesis) in a transgenic mouse model of CADASIL (TgNotch3R90C). The aim of this study was to determine how SCF+G-CSF promotes angiogenesis and whether SCF+G-CSF-enhanced angiogenesis is vitally involved in brain repair and cognitive improvement in TgNotch3R90C mice. To examine whether SCF+G-CSF-promoted angiogenesis is mediated by vascular endothelial growth factor (VEGF), Avastin, a drug for inhibiting angiogenesis by neutralizing biologic activity of VEGF, was given before SCF+G-CSF treatment. Water maze testing revealed that SCF+G-CSF-improved spatial learning and memory in TgNotch3R90C mice were prevented by Avastin. In addition, reduced cerebrovascular densities in TgNotch3R90C mice were restored by SCF+G-CSF treatment, whereas the SCF+G-CSF-enhanced angiogenesis was completely eliminated by Avastin. Moreover, Avastin also blocked the SCF+G-CSF-increased neural network rewiring (MAP2, SMI312, and GAP43 immunostaining), neurogenesis (Doublecortin immunostaining) and synaptogenesis (PSD95 and Synaptophysin immunostaining) in the brains of TgNotch3R90C mice. Furthermore, western blot data showed that VEGF expression was significantly decreased in cultured cerebral VSMCs of TgNotch3R90C mice and the whole brain of TgNotch3R90C mice compared to the age-matched wild type mice. SCF+G-CSF treatment enhanced the VEGF expression in both the cultured VSMCs and brain tissue of TgNotch3R90C mice. These findings suggest that SCF+G-CSF-increased VEGF may play a key role in enhancing cerebral angiogenesis, which is required for promoting brain repair and cognitive function in a mouse model of CADASIL. This study sheds light on how hematopoietic growth factors restrict CADASIL pathology.

This study was supported by American Heart Association (15GRNT25700284).